

# Gastrointestinal Intervention

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## Review Article

# Evaluation of malignant intraductal papillary mucinous neoplasms of the pancreas on computed tomography and magnetic resonance imaging



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## ABSTRACT

Preoperative cross-sectional imaging, such as computed tomography and magnetic resonance imaging, plays a key role in differentiating between benign and malignant intraductal papillary mucinous neoplasms. This article reviews the imaging features associated with malignant intraductal papillary mucinous neoplasm, as well as the recent studies validating the 2012 international consensus guidelines. This review also compared the diagnostic performance of computed tomography and magnetic resonance imaging in differentiating malignant from benign intraductal papillary mucinous neoplasms.

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Keywords: Computed tomography; Intraductal papillary mucinous neoplasm; Magnetic resonance imaging; Malignancy; Pancreas

## Introduction

Cystic lesions of the pancreas are increasingly being detected, due to the more widespread use of and advances in cross-sectional imaging and the increased frequency of health examinations. Although the exact incidence of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas has not been determined, IPMNs have been estimated to account for approximately 20% to 50% of all pancreatic cystic neoplasms.<sup>1,2</sup> IPMNs have been classified as branch duct (BD) type, main duct (MD) type, and combined or mixed type based on imaging findings and/or histology.<sup>3</sup> Computed tomography (CT) and magnetic resonance imaging (MRI), along with magnetic resonance cholangiopancreatography (MRCP), are the most useful radiologic methods for detecting IPMNs. Moreover, these imaging modalities are useful in distinguishing BD-IPMNs from other cystic lesions by showing multiplicity and a connection to the main pancreatic duct (MPD). As the management of IPMNs depends on their malignant potential, it is essential to accurately predict the risk of malignancy of each tumor on preoperative imaging.

## Radiologic Findings of Pancreatic IPMNs

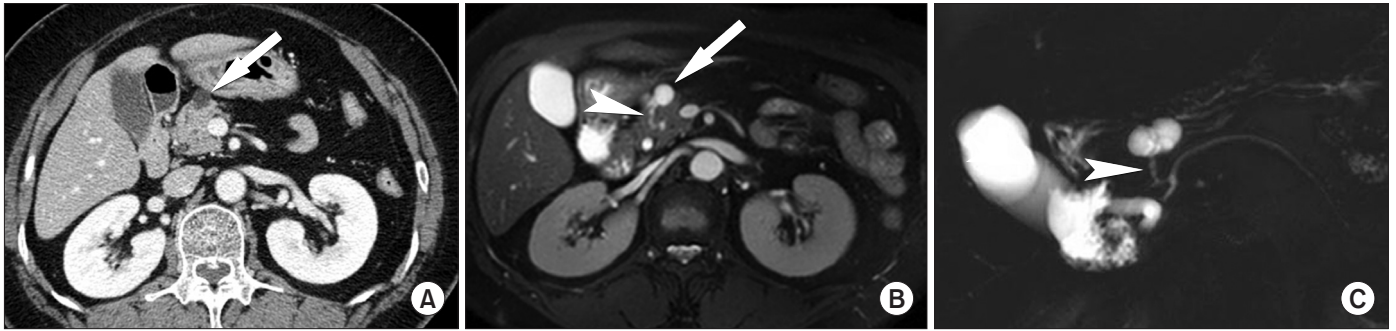
BD-IPMNs have been found to manifest as either grape-like clusters of cysts or cysts without dilatation of the MPD (Fig. 1).<sup>4</sup> Although BD-IPMNs may be located anywhere, the pancreatic head, especially the uncinate process is the most common site.<sup>4</sup> Of patients with BD-IPMN, 39%–64% have been found to show multiplicity.<sup>5,6</sup> Identification of the communication between the cystic lesion and the MPD is one of the most reliable findings for diagnosis of BD-IPMN. MRI with MRCP has shown better diagnostic performance than CT in differentiating IPMNs from other pancreatic cystic lesions by showing the ductal communication of cystic lesions with MPD.<sup>7–9</sup>

MD-IPMNs appear as dilated and tortuous MPDs, with the dilatation extending into the secondary branches that sometimes appear cystic (Fig. 2).<sup>4</sup> MD-IPMNs show a much higher malignant potential than BD-IPMNs (40%–95% vs 12%–62%).<sup>7,10–12</sup> According to recent International Association of Pancreatology guidelines,<sup>7</sup> the threshold of MPD for characterization of MD-IPMN has been lowered to > 5 mm in the absence of other causes of obstruction. MPD dilatation of 5–9 mm is considered a “worrisome

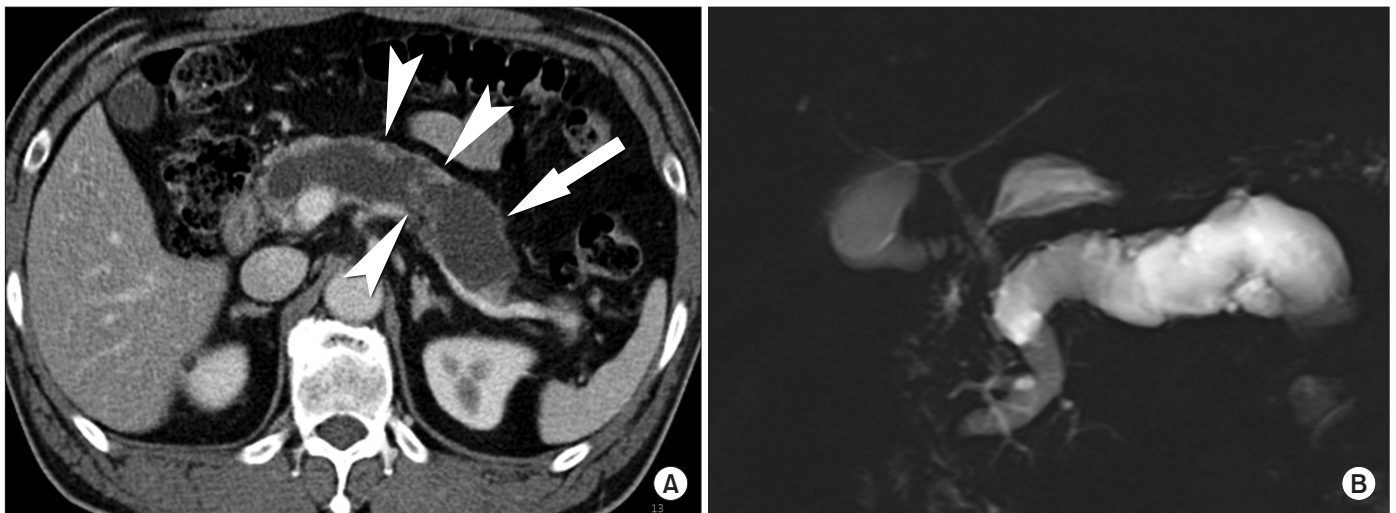
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Received August 27, 2015; Revised September 23, 2015; Accepted September 24, 2015

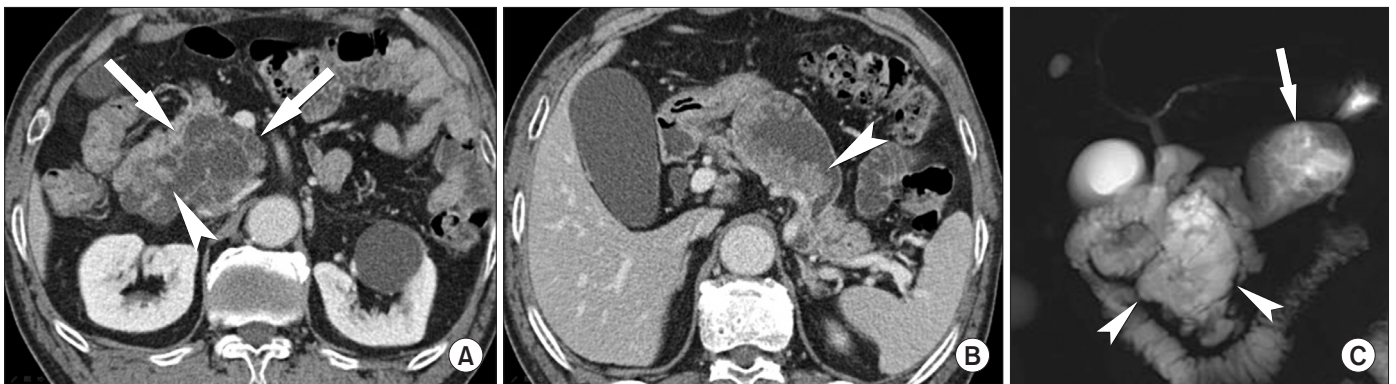
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**Fig. 1.** Branch duct type intraductal papillary mucinous neoplasm (IPMN) in a 60-year-old female. Contrast-enhanced computed tomography image (A) and T2-weighted magnetic resonance imaging (MRI) (B) show a small cystic lesion (arrows) in the pancreas head. A communication (arrowhead) between the cystic lesion and the main pancreatic duct is suspected on T2-weighted MRI. (C) Magnetic resonance cholangiopancreatography image demonstrates a communication (arrowhead) between the cystic lesion and the main pancreatic duct, suggesting a diagnosis of branch duct type IPMN.



**Fig. 2.** Main duct type intraductal papillary mucinous neoplasm (IPMN) in a 68-year-old male. (A) Contrast-enhanced computed tomography image shows marked dilatation of the main pancreatic duct (arrow) and several enhanced mural nodules (arrowheads) within the dilated main pancreatic duct. (B) Magnetic resonance cholangiopancreatography image shows the dilated and tortuous main pancreatic duct, suggesting main duct type IPMN.



**Fig. 3.** Combined type intraductal papillary mucinous neoplasm in a 74-year-old male. (A, B) Contrast-enhanced computed tomography images demonstrate lobulated cystic lesions (arrows) in the pancreas head and the dilated main pancreatic duct. Multifocal enhanced mural nodules (arrowheads) are observed within the cystic lesion and the dilated main pancreatic duct. (C) Magnetic resonance cholangiopancreatography image shows large lobulated cystic lesions (arrowheads) connecting to the tortuous, dilated main pancreatic duct (arrow).

feature”, while MPD diameters  $\geq 10$  mm are considered “high-risk stigmata”. However, the MPD in MD-IPMN can be dilated without neoplastic involvement, due to mucin, protein plugs, or focal pan-

creatitis.<sup>13</sup> Intralesional solid components can be observed, with calcification occurring in about 11% of these patients.<sup>14</sup> Dystrophic calcifications can be seen in the mucous material in dilated

MPDs.<sup>15</sup> The pancreas may appear enlarged and show signs of pancreatitis, or may be atrophic. Endoscopic retrograde cholangiopancreatography can show filling defects, representing tumors or inspissated mucus, within the dilated duct.<sup>15</sup>

Combined or mixed IPMN involves both the MPD and its BDs, with CT and MRI simultaneously showing findings of MD-IPMNs and BD-IPMNs (Fig. 3). The biologic characteristics of mixed IPMN may be similar to those of MD-IPMN.<sup>16</sup>

## Features Suggestive of Malignant IPMN

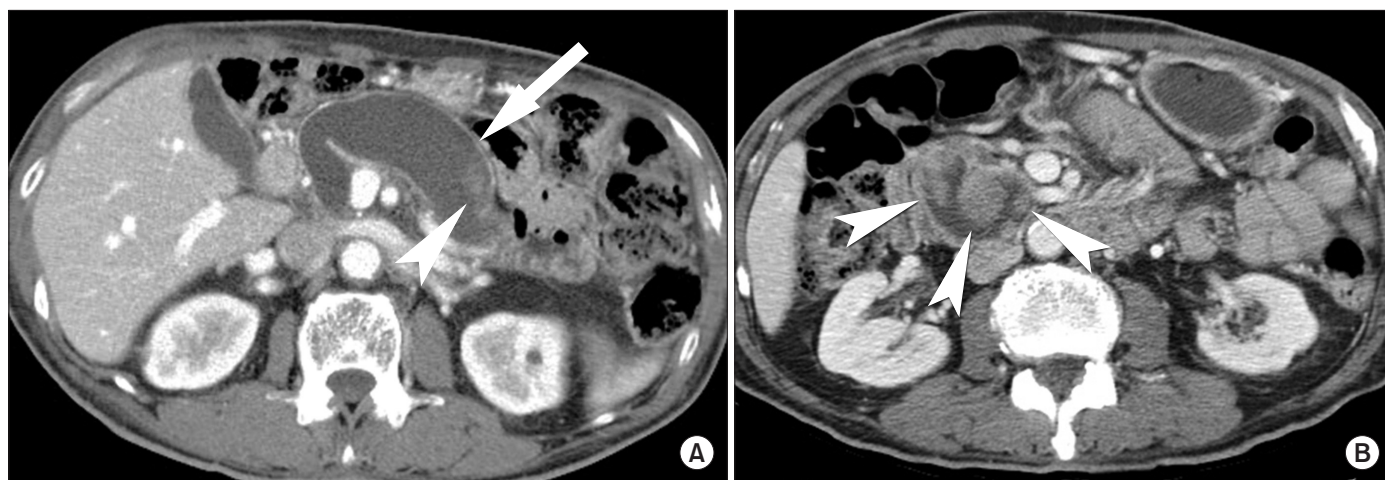
One of the most important issues regarding IPMN has been

the ability to predict malignancy. As described by the 2010 World Health Organization classification system,<sup>17</sup> IPMNs can be categorized into four subtypes: low-grade dysplasia, intermediate-grade dysplasia, high-grade dysplasia, and invasive carcinoma associated with IPMN. In most studies, malignant IPMN is defined as high-grade dysplasia and invasive carcinoma, inasmuch as surgical resection has been recommended for both.<sup>7,18</sup> The imaging features suggestive of malignant IPMN of the pancreas are summarized in Table 1.

**Table 1** Imaging Features Suggestive of Malignant IPMN of the Pancreas

Imaging features	Description	The 2012 guideline	
		High-risk stigmata	Worrisome feature
Presence of mural nodule/solid component	Presence of mural nodule is the most important predictors of malignancy.	Enhanced mural nodule	Non-enhanced mural nodule
Large size of mural nodule/solid mass	A large size of mural nodule/solid mass is associated with malignancy (threshold nodule size, 5–10 mm).		
Involvement of MPD	Main duct type or mixed type IPMN has much higher malignant potential than BD-IPMN.		
Large size of MPD diameter	Marked MPD dilatation is associated with malignancy.	MPD $\geq 10$ mm	MPD of 5–9 mm
Size of cystic lesion	The cystic size $> 3$ cm have been reported a malignant feature in BD-IPMN.		Included
Thick septa or cystic wall	Thick septa or cystic wall is associated with malignancy.		Included
Lymphadenopathy	The definition and significance of lymphadenopathy remain unclear.		Included
Abrupt MPD change with distal pancreatic atrophy	The significance of abrupt MPD change with distal pancreatic atrophy remains unclear.		Included
Biliary obstruction	Biliary dilatation is associated with malignancy of cystic lesion in the pancreas head.	Obstructive jaundice	
Invasion of vascular or adjacent structures	Invasion of vascular or adjacent structures is associated with malignancy.		
Intralesional calcification	Intralesional calcification has been reported to be a malignant predictor, but controversy exists.		

IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; BD-IPMN, branch duct type IPMN.



**Fig. 4.** Main duct type intraductal papillary mucinous neoplasm (IPMN) with high-risk stigmata (enhanced solid component and main pancreatic duct diameter  $\geq 10$  mm) in a 73-year-old male. (A, B) Contrast-enhanced computed tomography images show a diffusely dilated main pancreatic duct (arrow) with a diameter up to 23 mm and several enhanced solid mural nodules (arrowheads) within the dilated main pancreatic duct. The pathologic diagnosis was main duct type IPMN with associated invasive carcinoma.



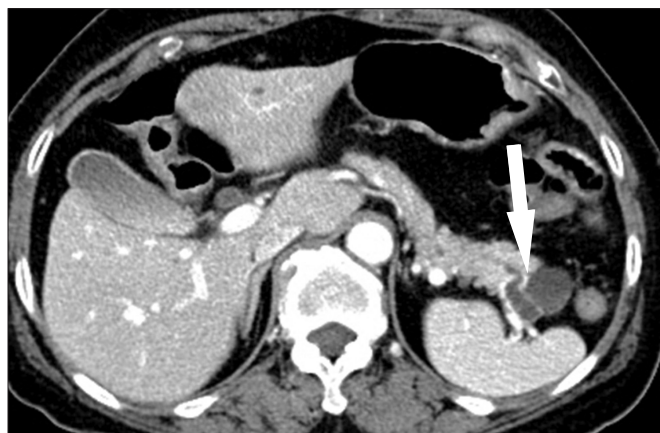
# The 2012 international consensus guidelines

Recently, the working group of the International Association of Pancreatology updated international consensus guidelines for the management of IPMNs and mucinous cystic neoplasms

of the pancreas.<sup>7</sup> These 2012 guidelines have classified “high-risk stigmata” as enhanced solid component on CT or MRI along with an MPD diameter  $\geq 10$  mm (Fig. 4). “Worrisome features” include cysts  $\geq 3$  cm in diameter, thickened enhanced cyst walls, MPD diameters of 5–9 mm, non-enhanced mural nodules, abrupt



**Fig. 5.** Branch duct type intraductal papillary mucinous neoplasm (IPMN) with a worrisome feature (cyst  $\geq 3$  cm in diameter) in a 63-year-old female. Contrast-enhanced computed tomography image shows a 4-cm lobulated cystic lesion (arrow) in the pancreas head, which was pathologically confirmed as branch duct type IPMN with low-grade dysplasia.



**Fig. 6.** Branch duct type intraductal papillary mucinous neoplasm (IPMN) with a worrisome feature (thickened enhanced septum) in a 73-year-old female. Contrast-enhanced computed tomography image demonstrates a 2.5-cm cystic lesion with a thickened enhanced septum (arrow) in the pancreas tail, which was pathologically confirmed as branch duct type IPMN with low-grade dysplasia.



**Fig. 7.** Combined type intraductal papillary mucinous neoplasm (IPMN) with two worrisome features (main pancreatic duct 5–9 mm in diameter and lymphadenopathy) in a 73-year-old male. (A–C) Contrast-enhanced computed tomography images demonstrate mild dilatation of the main pancreatic duct (A, arrow), measuring 6 mm in diameter, and several cystic lesions (B, arrow) in the pancreas tail. Several borderline-sized lymph nodes (arrowheads) are observed in the hepatoduodenal ligament (A), peripancreatic area (B), and gastrohepatic ligament (C). The pathologic diagnosis was combined type IPMN with intermediate-grade dysplasia.



**Fig. 8.** Main duct type intraductal papillary mucinous neoplasm (IPMN) with a worrisome feature (abrupt change in main pancreatic duct caliber with distal pancreatic atrophy) in a 75-year-old female. (A, B) Contrast-enhanced computed tomography images show abrupt main pancreatic duct dilatation (arrows) in the pancreas tail with distal pancreatic atrophy (arrowhead). (C) Magnetic resonance cholangiopancreatography image also shows abrupt changes in main pancreatic duct diameter in the pancreas tail. The pathologic diagnosis was main duct type IPMN with intermediate-grade dysplasia.

change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy (Fig. 5–8). Resection is recommended in all surgically fit patients with MD-IPMN and BD-IPMN having “high-risk stigmata”. By contrast, further evaluation by endoscopic ultrasonography (EUS) is recommended for BD-IPMNs with “worrisome features”, thereby stratifying the risk of malignancy.

Several studies have evaluated the clinical utility of these 2012 guidelines.<sup>10,19,20</sup> In a recent systematic review validating the 2012 guidelines in 1,382 surgically resected patients,<sup>20</sup> a pooled analysis showed that there were 362 (36.2%) malignant IPMNs in 1,000 patients with high risk and worrisome features, and 342 (89.5%) benign IPMNs in 382 patients without high risk/worrisome features. The positive predictive values (PPVs) of the high risk and worrisome risk groups were 65.8% (104/158) and 28.7% (75/261), respectively.<sup>20</sup> In a recent study by our group,<sup>10</sup> 60 patients with surgically confirmed BD-IPMNs and 98 with confirmed MD-IPMNs were further evaluated by both CT and MRI. For BD-IPMNs, the sensitivity and specificity of overall significant findings on univariate analyses (i.e., mural nodule, thick septa, and MPD size  $\geq 5$  mm) for predicting malignancy on both CT and MRI were 87.5% and 75.0%, respectively. For MD-IPMNs, the sensitivity and specificity of overall significant findings (i.e., presence of mural nodules and enhancement, lymphadenopathy, and mural nodule size  $> 7$  or 8 mm) were 72.7% and 75.9%, respectively, on CT, and 77.3% and 81.5%, respectively, on MRI.<sup>10</sup> Using the criterion of the presence of at least one worrisome feature or high risk stigmata in BD-IPMN, CT had a PPV and negative predictive value (NPV) of 23.3% and 96.7%, respectively, whereas MRI had a PPV and NPV of 20.0% and 96.0%, respectively. For MD-IPMN, the PPV and NPV were 47.7% and 80.0%, respectively, for CT, and 45.7% and 66.7%, respectively, for MRI. The PPVs of high risk stigmata or worrisome features in this study were relatively low, consistent with the results of the recent systematic review.<sup>20</sup> Another study, in which 98 patients with pathologically confirmed IPMN were evaluated using MRI and MRCP, found that the sensitivity and specificity of the 2012 guidelines by three readers were 79%–90% and 24%–80%, respectively.<sup>19</sup>

### Presence of solid mural nodules

The presence of solid mural nodules is one of the most important predictors of malignancy of IPMNs (Fig. 4).<sup>10–12,21,22</sup> In a recent meta-analysis, the presence of mural nodules had the highest diagnostic odds ratio (OR) of 6.0 for malignant BD-IPMNs.<sup>12</sup> Another meta-analysis also reported that the presence of mural nodules had an OR of 9.3 for malignancy of IPMNs.<sup>23</sup> The 2012 guidelines differentiated mural nodules by the presence or absence of enhancement.<sup>7</sup> Enhanced mural nodules are defined as “high-risk stigmata”, while non-enhanced mural nodules are regarded as “worrisome features”. Our recent study found that 52 among 53 mural nodules in pancreatic IPMNs were enhanced.<sup>10</sup> Although mural nodules attach to the cystic wall and may be located in non-dependent positions,<sup>24,25</sup> differentiating non-enhanced mural nodules from mucin components or internal debris may sometimes be difficult. Additional studies are needed to determine the significance of non-enhanced mural nodules.

### Size of mural nodules

Large size of mural nodules has also been reported to be associated with malignant IPMN. The cutoff value of mural nodule size for predicting malignancy has been found to range from 5 mm to 10 mm. Mural nodule size  $> 7$  mm on EUS showed a

sensitivity of 74.3% and a specificity of 72.7% for predicting malignancy.<sup>26</sup> Another study showed that mural nodules  $> 5$  mm in BD-IPMN on EUS were one of the most important factors predicting malignancy.<sup>27</sup> In our previous study using preoperative cross-sectional imaging, cutoff values of 8 mm on CT and 7 mm on MRI enhanced diagnostic performance, especially the specificity for diagnosis of malignant IPMN.<sup>10</sup>

### Dilatation of the main pancreatic duct

The 2012 guidelines define MPD sizes of  $\geq 10$  mm and 5–9 mm as “high-risk stigmata” and “worrisome features”, respectively (Fig. 4, 7).<sup>7</sup> Many studies have reported that marked dilatation of the MPD is associated with malignant IPMN.<sup>12,22,23,28,29</sup> A recent meta-analysis assessing characteristics of BD-IPMN associated with malignancy<sup>30,31</sup> reported that MPD  $> 6$  mm or 5–9 mm showed the second highest diagnostic performance after the presence of a mural nodule. By contrast, MPD size criteria of 10 mm have been a source of controversy. MPD  $> 10$  mm was not a significant predictor of malignancy in both MD- and BD-IPMNs in our previous study.<sup>10</sup> Other studies also demonstrated that MPD  $> 10$  mm was not significantly different between benign and malignant IPMNs.<sup>18,32</sup> The significance of MPD size in MD-IPMN is also questionable.<sup>33,34</sup> A recent study suggested that MPD size did not correlate with malignant potential in MD-IPMN because MD-IPMNs with MPD  $< 5$  mm still had substantial malignant potential.<sup>34</sup>

### Large cyst size ( $> 3$ cm)

Although the 2006 guidelines suggested that cyst size  $> 3$  cm is a malignant feature in BD-IPMNs,<sup>3,23,29,35,36</sup> its significance remains unclear (Fig. 5). Several recent studies found no significant differences in malignancy between cysts  $< 3$  cm and  $\geq 3$  cm.<sup>10,11,19,27,37</sup> A meta-analysis of patients with BD-IPMN and the 2012 guidelines suggested that BD-IPMNs  $> 3$  cm without other features associated with malignancy may not indicate the need for immediate surgical resection, particularly in elderly patients.<sup>12</sup>

### Other findings

A meta-analysis found that thick septa or cystic walls were significantly associated with malignant BD-IPMN (Fig. 6).<sup>12</sup> However, its absolute diagnostic value was fairly weak, with a pooled sensitivity and specificity of 58% and 60%, respectively.<sup>12</sup> Our previous study showed that the presence of thick septa was a significant predictor for malignancy in BD-IPMN on univariate analysis, but not on multivariable analysis, and was not a significant predictor of malignancy in MD-IPMN.<sup>10</sup> The vagueness of this criterion suggests the need for more accurate definition and further studies evaluating its diagnostic performance.

The significance of lymphadenopathy remains unclear (Fig. 7).<sup>10,18,21</sup> Our previous study found that lymphadenopathy was a significant predictor for malignant MD-IPMN, with high specificity (92.6% for CT and 96.3% for MRI) and relatively low sensitivity (34.1% for CT and 29.6% for MRI).<sup>10</sup> In another study involving 350 BD-IPMNs, lymphadenopathy was significant only in univariate analysis, with a sensitivity of 7.2% and a specificity of 99.6%, but not in multivariable analysis.<sup>21</sup> By contrast, a study of 114 mucinous cystic lesions of the pancreas found that lymphadenopathy did not differ significantly between benign and malignant lesions.<sup>18</sup> One possible explanation for these discrepancies may be the lack of an accurate definition of lymphadenopathy in



IPMN.

The 2012 guidelines define an abrupt change in MPD diameter with distal pancreatic atrophy as a worrisome feature (Fig. 8).<sup>7</sup> Distal pancreatic atrophy is defined as a ratio of MPD diameter to the width of the pancreatic parenchyma at the same level greater than 0.5.<sup>10,38</sup> However, studies found that this finding was not a significant predictor of malignant IPMN.<sup>10,18,21</sup>

Other reported imaging features of malignant IPMN which were not suggested in the 2012 guidelines include solid mass invading adjacent structure, presence of vascular invasion or distant metastasis.<sup>8,28</sup> Biliary dilatation or CBD obstruction can be caused by direct tumor invasion or retention of mucin.<sup>28</sup> Many studies demonstrated significant correlation between biliary dilatation and malignant IPMN.<sup>14,39,40</sup> Obstructive jaundice, which is the clinical presentation of biliary obstruction, is one of “high-risk stigmata” in the 2012 guidelines. Intralesional or intraductal calcifications were reported to be associated with malignancy in several studies, and showed sensitivity of 18%–33% and specificity of 77%–87%.<sup>14,22</sup> However, another study did not find significant difference in the presence of calcification between benign and malignant IPMNs.<sup>40</sup> Regarding location of the cystic lesion, majority of studies showed no significant correlation between location of the lesion and malignant potential,<sup>41–43</sup> although a few studies reported that malignant IPMNs were most frequent in the pancreas head.<sup>29,44</sup>

## Diagnostic Performance of CT and MRI

The 2012 guidelines recommend either CT or MRI with MRCP for evaluation of pancreatic cystic lesions larger than 1 cm.<sup>7</sup> In our previous study involving 158 patients with both CT and MRI, CT and MRI with MRCP showed comparable good performance for diagnosing malignancy in both BD-IPMN and MD-IPMN, with both CT and MRI showing accuracies of 76.7%–78.3% for BD-IPMN, and these two modalities showing accuracies of 74.5% and 79.6%, respectively, for MD-IPMN.<sup>10</sup> A previous study with 25 IPMNs also demonstrated that CT and MRCP showed similar sensitivity and specificity for evaluating mural nodules, MPD > 10 mm, thick septa, and calcifications.<sup>45</sup> However, a recent study with 60 IPMNs showed that MRI was slightly superior to CT in diagnosing malignancy, with accuracies of 92% and 86%, respectively, although the difference was not statistically significant.<sup>32</sup> Moreover, MRI showed a trend towards significance for predicting malignancy with increasing size of mural nodules, while CT did not show such correlation.<sup>32</sup> Technological improvements in both CT and MRI, including thinner slice thicknesses and higher temporal and spatial resolution, may improve their diagnostic performance over time.

## Conclusion

In summary, the presence of solid mural nodules is thought to be the most important predictor of malignancy in IPMN. Overall findings using the 2012 guidelines demonstrated acceptable sensitivity and specificity. However, these guidelines resulted in a relatively low PPV, suggesting the need for further investigation and modification. In addition, several worrisome features, including thickened septa or cystic walls, lymphadenopathy, and distal pancreatic atrophy, should be defined more precisely. Both CT and MRI have shown good diagnostic performance for predicting malignant IPMN, and their ability may be further improved by further technological developments.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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